Concomitant coronary and peripheral arterial disease: Relationship between the inflammatory status of the affected limb and the severity of coronary artery disease

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Objective: **In coronary artery disease (CAD), concomitant peripheral arterial disease (PAD) entails increased systemic inflammatory profile and more severe coronary atherosclerosis. We investigated the relationship between the inflammatory status in the affected limb and CAD severity.**
Methods: **In 46 CAD+PAD and 31 CAD-alone patients, the inflammatory status of the leg circulation was measured by the transfemoral gradients of neutrophil myeloperoxidase (MPOx) content and interleukin-6 (IL-6). CAD severity was defined by evaluating coronary artery endothelial function, number of significant coronary stenoses, and prevalence of three-vessel CAD and myocardial infarction (MI).**
Results: **In the affected limb of CAD+PAD patients, the transfemoral gradients of neutrophil MPOx content and IL-6 were higher ($P < .01$, for both) than in the healthy leg of CAD-only patients. At multivariate analysis, CAD+PAD patients with transfemoral gradients of MPOx and IL-6 > median had a more compromised coronary artery endothelial function ($P < .05$, for both). Furthermore, CAD+PAD patients with transfemoral gradients of neutrophil MPOx content > median showed an independent association with a greater number of significant coronary stenoses, and a greater prevalence of three-vessel CAD and previous MI ($P < .01$, for all). A more severe coronary atherosclerosis was observed also in CAD+PAD patients with transfemoral gradients of IL-6 > median vs those with IL-6 < median, although differences were not statistically significant.**
Conclusion: **In CAD patients, the coexistence of PAD does not necessarily entail a more severe coronary atherosclerosis. Only those with an inflammatory status of the affected limb presents more severe CAD. Future studies will clarify whether the presence of peripheral inflammation plays a mechanistic role in CAD evolution. (J Vasc Surg 2009;49:1465-71.)**

In patients with coronary artery disease (CAD), a coexistent peripheral arterial disease (PAD) entails a higher mortality risk.[1-4] This could reflect the finding that coronary atherosclerosis is more severe in CAD+PAD than in CAD-alone patients.[5-7] Indeed, apart from being older, CAD patients with PAD have a higher prevalence of diabetes mellitus and hypertension than those without PAD,[3-6] but the greater atherosclerotic coronary artery burden appears to be unrelated to classic risk factors.[5,6] Thus, other mechanisms may be involved. We have recently reported that in CAD+PAD patients increased gradients of neutrophil myeloperoxidase (MPOx) content and interleukin-6 (IL-6) across the femoral circulation of the affected limb are strongly associated with impaired coronary artery endothelial function.[8] Furthermore, serum from the claudicant limb of CAD+PAD patients induced, in vitro, a significantly greater release of monocyte chemoattractant protein-1 (MCP-1) from human coronary artery endothelial cells (HCAECs) vs serum from the aorta of the same patients.[8] The difference disappeared when HCAECs were incubated with serum from CAD-alone patients. Collectively, these findings suggest that in PAD circulatory triggers originated from the affected limb could activate the endothelium at distant sites. Given the atherogenic potential of endothelial dysfunction, the present study was designed to determine whether there is a relationship between the degree of peripheral arterial inflammation and the severity of CAD.

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MATERIALS AND METHODS

Patients. In addition to the 40 patients included in the original paper,[8] we studied 37 more subjects admitted to our department for elective coronary angiography because the evidence of inducible myocardial ischemia during stress tests. Therefore, the present study includes 46 PAD+CAD and 31 CAD-alone patients. PAD+CAD patients had an ankle-brachial index (ABI) <0.90 and referred a history of intermittent claudication lasting at least 1 year. None had critical limb ischemia. In CAD-alone patients, PAD was excluded on the basis of echo-color-Doppler examination and ABI >0.90. Patients with ABI ≥1.4 were excluded. Other exclusion criteria were: a history of trauma, surgery, or myocardial infarction (MI) in the previous 3 months, a previous coronary or peripheral artery revascularization procedure, unstable angina, malignant disease, acute and

chronic renal, pulmonary, and hepatic diseases, and any other pathologic condition associated with inflammation. No patient was taking anti-inflammatory drugs other than aspirin as an antiplatelet agent. All drugs were discontinued for 18 hours or longer before the study, which was performed in the morning after an overnight fast. All patients gave their informed written consent to the protocol which was approved by the Ethics Committee of our institution.

Methods. In each patient, clinical history and risk factors were assessed. Smokers included current and former smokers. Hypertension was diagnosed if systolic arterial pressure exceeded 140 mm Hg and/or diastolic arterial pressure exceeded 90 mm Hg, or if the patient used antihypertensive drugs. Hypercholesterolemia was diagnosed if plasma total cholesterol exceeded 240 mg/dL or plasma low-density lipoprotein (LDL) cholesterol exceeded 130 mg/dL or if the patient used lipid-lowering drugs because of a history of hypercholesterolemia. Diabetes mellitus was diagnosed if plasma fasting glucose exceeded 126 mg/dL or if the patient used hypoglycemic agents.

To assess the inflammatory status of the affected limb, before angiography all subjects underwent simultaneous blood sampling from the femoral vein (in the case of CAD+PAD the femoral vein was that of the claudicant limb), aorta, coronary sinus, and an antecubital vein for the measurement of neutrophil MPOx content, and plasma levels of IL-6 and high sensitivity (hs) C-reactive protein (CRP). The neutrophil MPOx content was determined by a Bayer H*1 analyzer (Bayer Diagnostic Division, Tarrytown, NY) which calculates an MPOx index of the mean neutrophil MPOx content as described elsewhere.[9] Positive values represent MPOx-rich neutrophils, and negative values represent neutrophils depleted of MPOx consequent to neutrophil activation. Thus, a lower MPOx index in blood from the femoral vein, as compared with the aorta, represented an index of neutrophil activation through the femoral vascular bed. Plasma levels of IL-6 were measured by a high-sensitive ELISA method (Dade Behring Diagnostics, Deerfield, Ill). CRP was determined using an hs assay (Dade Behring Diagnostics).

To assess CAD severity we measured: (1) the endothelial function of the epicardial arteries by evaluating their vasomotor response to the cold pressor test (CPT); (2) the number of stenosis >50% in the major coronary arteries; (3) the prevalence of three-vessel CAD; and (4) the prevalence of previous MI.

Coronary artery endothelial function was measured as follows. After a baseline left coronary angiogram, the patient immersed the right hand in iced water for 90 seconds and a second coronary angiogram was recorded to evaluate the coronary artery endothelial vasoreactivity to the CPT. In each patient, an average of 3.2 segments were selected in one projection on the baseline angiogram. The left anterior descending coronary artery was used as the experimental artery. Three coronary segments were considered: proximal (from the ostium to first septal branch), mid (from the first to second septal branch), and distal (after the second septal branch). The presence of coronary stenosis was defined as the percentage of diameter stenosis above 50. In stenotic coronary arteries, whenever possible, at least one segment proximal and one segment distal to the stenosis were obtained. In case of ostial stenosis, two or more segments distal to the stenosis were obtained. The luminal diameter (LD) was measured at end diastole by quantitative coronary angiography using the catheter as a scaling device. In case of stenotic coronary arteries, changes in LD of the stenosis itself were analyzed separately from the changes of the adjacent reference segments. The data from the stenotic and adjacent reference segments were pooled because there was a uniform response to the CPT. Data are presented as average of % LD changes of coronary segments after CPT compared to baseline.

To ensure proper filling of the coronaries with contrast medium, an angioplasty guide catheter was used in each case and an automated contrast delivery system was used to inject the same contrast volume at the various steps of the experimental protocol (Acist Medical Systems, Eden Prairie, Minn). The identical projection was used for the analysis of the same segments at the different stages of the protocol. Angiograms were recorded at 25 frames/second. Heart rate and blood pressures were recorded during the entire study protocol. The contrast medium used was the nonionic monomer, hypo-osmolar (Iomeron 400, Bracco, Italy).

Noteworthy, in the first 40 patients of our series (22 CAD+PAD and 18 CAD-alone) the relationship between inflammation of the affected limb and coronary artery endothelial function has been previously reported.[8] In the present paper, we doubled the CAD+PAD population, increased the CAD-alone group and, in addition to evaluate coronary artery endothelial function, we investigated other measures of CAD severity in the entire population.

Statistical analysis. Inflammatory parameters and continuous variables of CAD severity (number of significant coronary artery stenoses and coronary artery endothelial function), which were not normally distributed, were expressed as median and interquartile range and analyzed by non parametric tests. The Friedman test and the Wilcoxon test were used for intra-group comparisons, and the Kruskal-Wallis and the Mann-Whitney *U* tests for intergroup comparisons. Categorical variables were compared by χ^2 test. Correlations were tested with the Spearman method. Multivariate regression analyses adjusted for age, gender, smoke, hypercholesterolemia, hypertension, and diabetes mellitus were used to assess the association of the extent of inflammation in the affected limb with the measures of CAD severity as dependent variables. In particular, linear logistic regression analysis was used when the dependent variable was continuous (coronary artery endothelial function and number of significant coronary stenoses), while binary logistic analysis when the dependent variable was categorical (prevalence of three-vessel CAD and previous MI).

Table I. Patients' characteristics

	CAD+PAD (n = 46)	*CAD (n = 31)*	P *value*
Age (year)	63.0 ± 8.5	64.2 ± 5.7	.59
Gender (males)	38 (83)	24 (77)	.57
Hypertension (%)	31 (67)	23 (74)	.53
Hypercholesterolemia (%)	34 (74)	25 (81)	.49
Diabetes mellitus (%)	12 (26)	7 (23)	.73
Smoking (%)	40 (87)	23 (74)	.15
ABI	0.62 ± 0.10	1.13 ± 0.10	<.01
Previous MI	25 (54%)	12 (39%)	.18
Treatments			
Antiplatelets (%)	40 (87)	26 (84)	.70
Statins (%)	31 (77)	21 (74)	.97
ACE-inhibitor (%)	22 (48)	15 (48)	.96
Beta-blockers (%)	8 (17)	7 (23)	.53
Calcium-antagonists (%)	13 (28)	12 (39)	.34
Nitrates (%)	11 (24)	9 (29)	.61

CAD, Coronary artery disease; *PAD,* peripheral arterial disease; *ABI,* ankle-brachial index; *MI,* myocardial infarction; *ACE,* angiotensin converting enzyme.

RESULTS

Table I shows the characteristics of the study population.

Peripheral vascular inflammation. As Table II shows, there was a significant transfemoral decrease in the MPOx index in the affected limb of CAD+PAD patients. Actually, median neutrophil MPOx content was −2.7 (range −4.8 to 1.4) in the aorta and −4.3 (range −7.0 to −1.0) in the femoral vein ($P < .01$). Conversely, the neutrophil MPOx content in aortic blood was similar to that in the coronary sinus and in the antecubital vein. Therefore, as Fig 1 shows, the venous-arterial (V-A) difference in MPOx content across the femoral circulation (median −1.6 [range −2.9 to −0.2]) was significantly greater than that across the coronary (median 0.0 [range −1.6 to 1.2], $P < .01$) and the upper limb circulation (median −0.4 [range −1.3 to 0.2], $P < .01$). Furthermore, the change in MPOx content in the transfemoral circulation of affected legs was significantly greater than that in the transfemoral circulation of the healthy legs of CAD patients without PAD (median −0.1 [range −0.2 to 0.4], $P < .01$). In the latter group, the MPOx content in the aorta was similar to that in the other vascular districts (Table II).

Also plasma levels of IL-6 were higher in femoral venous blood than in aortic blood (Table II). Differentially, IL-6 levels in venous blood from the coronary sinus and antecubital vein did not differ from those in aortic blood (Table II). Thus, as Fig 1 shows, the IL-6 V-A difference across the femoral circulation (median 0.18 [range 0.0 to 0.43] pg/mL) was greater than that across both coronary (median 0.0 [range −0.2 to 0.1] pg/mL, $P < .01$) and upper limb circulation (median −0.1 [range −0.3 to 0.1] pg/mL, $P < .01$). It was also greater than that across the femoral circulation of the legs of CAD-only patients (median 0.0 [range −0.2 to 0.1] pg/mL, $P < .01$).

Contrary to what was observed for MPOx and IL-6, the venous arterial difference in hs-CRP across the femoral circulation of the affected limb was similar to that of the other vascular districts (Table II).

In CAD+PAD patients, there was no relationship between the ABI and the transfemoral V-A differences of plasma levels of IL-6 ($P = -.13$), neutrophil MPOx content ($P = .07$) and CRP ($P = -.24$).

Peripheral vascular inflammation and coronary artery endothelial function. Coronary artery endothelial function tended to be lower in CAD+PAD than in CAD-alone patients (median 0.0 [range −1.8 to 2.0] vs 3.0 [−3.0; 6.0] %; $P = .16$). As shown in Fig 2, coronary artery endothelial function progressively decreased from CAD-alone patients (median 3.0 [range −3.0 to 6.0] %), CAD+PAD patients with transfemoral gradient of MPOx < median (median 1.0 [range 1.0 to 11.0] %) to CAD+PAD patients with transfemoral gradient of MPOx > median (median −1.8 [range −10.6 to −1.0] %) (P for trend < .01). The corresponding values for IL-6 were 3.0 (range −3.0 to 6.0) %, 2.0 (range −1.0 to 6.0) %, and −2.0 (range −13.8 to 0.5) % (P for trend < .05) (Fig 3). At Mann-Whitney U test, coronary artery endothelial function was significantly more compromised in CAD+PAD patients with transfemoral gradients of both MPOx and IL-6 > median than in the other two groups (Figs 2 and 3). Conversely, coronary artery endothelial function was similar in CAD+PAD patients categorized according to the median value of transfemoral gradient of CRP and in CAD-alone patients (data not shown).

In CAD+PAD, coronary artery endothelial function correlated with transfemoral (V-A) difference of leukocyte MPOx content ($P = .65$, $P < .01$) and IL-6 plasma levels ($P = .53$, $P < .01$), but not with that of hs-CRP. Even more important, in the CAD+PAD group, linear regression analyses showed that the transfemoral gradient of both MPOx and IL-6 were the only variables significantly associated with coronary artery endothelial function after adjustment for age, gender, and risk factors (β coefficient 0.53, 95% confidence interval [CI] 1.48-14.66, $P < .01$ for MPOx and β coefficient −0.36, 95% CI −11.73-0.91, $P < .01$ for IL-6). There was no relationship between coronary artery endothelial function and the transcoronary gradient of MPOx, IL-6, and hs-CRP.

Coronary artery endothelial function was not related to inflammatory parameters in the CAD-only group. The percentage increase in luminal diameter after nitroglycerin was similar in the two groups.

Peripheral vascular inflammation and number of significant coronary artery stenoses. The number of coronary artery stenoses >50% was greater in CAD+PAD patients with transfemoral gradients of MPOx > median (median 4.0 [range 3.5 to 4.5]) vs both CAD+PAD patients with less peripheral vascular inflammation (median 2.5 [range 1.0 to 3.0]) ($P < .01$) and CAD-alone patients (median 2.0 [range 1.0 to 4.0]) ($P < .01$) (P for trend < .05) (Fig 2). The corresponding values for IL-6 were 4.0 (range 2.0 to 4.0); 3.0 (range 1.0 to 4.0); 2.0 (range 1.0 to 4.0) (Fig 3), thus showing a trend similar to that observed for MPOx. However, at Kruskal-Wallis test, differences did

Table II. Inflammatory markers measured in four vascular districts

	Aorta	*Coronary sinus vein*	*Antecubital vein*	*Femoral vein*
		MPOx index		
CAD	−1.8 (−5.6; 0.2)	−1.1 (−1.9; 1.5)	−2.1 (−5.4; −0.4)	−1.9 (−6.6; 0.65)
CAD+PAD	−2.7 (−4.8; 1.4)	−2.2 (−4.5; 1.3)	−3.4 (−5.4; 0.4)	−4.3 (−7.2; −1.0)*
		Plasma levels of IL-6 (pg/mL)		
CAD	1.5 (0.9; 1.7)	1.3 (0.9; 1.8)	1.5 (1.1; 1.7)	1.4 (1.0; 1.7)
CAD+PAD	1.4 (0.9; 3.1)	1.60 (1.1; 2.6)	1.52 (0.8; 3.1)	1.7 (1.0; 3.1)*
		Plasma levels of hs-CRP (mg/L)		
CAD	1.1 (0.4; 1.9)	0.5 (0.4; 1.5)	1.0 (0.3; 1.9)	1.1 (0.5; 1.9)
CAD+PAD	2.3 (1.1; 5.8)	2.3 (1.1; 5.1)	2.5 (1.3; 5.6)	2.1 (1.3; 5.4)

CAD, Coronary artery disease; *PAD,* peripheral arterial disease; *MPOx,* neutrophil myeloperoxidase; *IL-6,* interleukin-6; *hs-CRP,* high sensitivity C-reactive protein.
*Significantly greater than in aorta ($P < .01$).

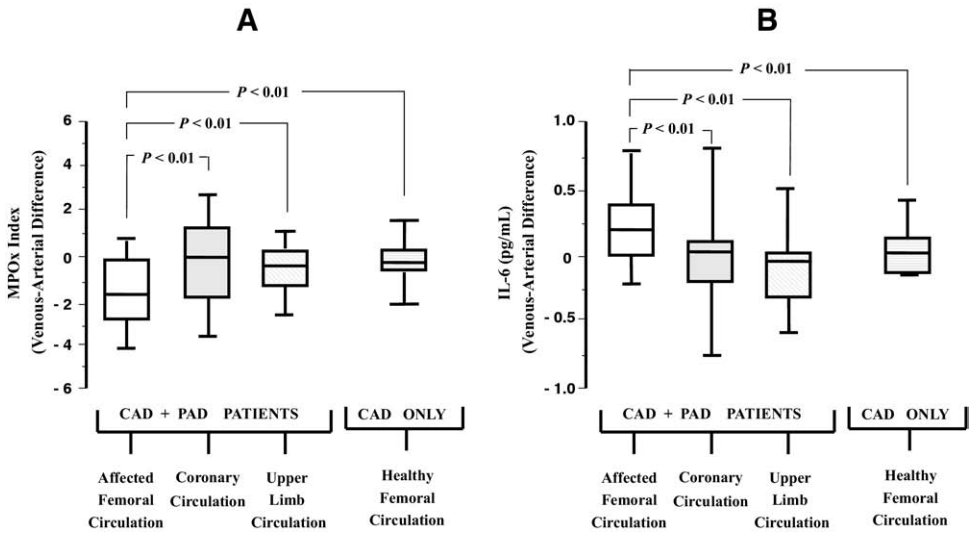

Fig 1. Venous-arterial differences in neutrophil myeloperoxidase (MPOx) content **(A)** and interleukin-6 (IL-6) **(B)** across femoral, coronary, and upper limb vascular beds. Data are expressed as medians, with 25th and 75th percentiles (*boxes*), and 10th and 90th percentiles (*bars*). In the coronary artery disease + peripheral arterial disease (CAD+PAD) group, the differences in MPOx content and IL-6 across the femoral circulation of the affected leg were significantly greater than that across the coronary circulation and the circulation of the upper limb. They were also greater than that across the femoral circulation of the healthy leg of CAD patients without PAD.

not reach the statistical significance (P for trend = .14). Noteworthy, an increased transfemoral gradient of MPOx remained significantly associated with a higher number of coronary stenoses after adjustment for classic risk factors (β coefficient 0.53, 95% CI 0.65-2.56; $P < .05$).

Peripheral vascular inflammation and prevalence of three-vessel CAD. As shown in Fig 2, even the prevalence of three-vessel CAD was greater in CAD+PAD patients with transfemoral neutrophil activation (17/24; 71%) than in the other two groups (6/22 [27%] in patients with lower neutrophil activation [$P < .01$], and 11/31 [35%] in those with CAD-alone [$P < .05$]). For IL-6 there was a progressive increase in the prevalence of three-vessel CAD from patients with CAD-alone (11/31, 35%) CAD+PAD patients with transfemoral gradient of IL-6 < median (10/23, 43%) to CAD+PAD patients with IL-6 transfemoral gradient > median (13/23, 57%) (Fig 3). However, group difference was not statistically significant (P for trend = .32). At multivariate analysis, the transfemoral gradient of MPOx resulted independently associated with the presence of three-vessel CAD (odds ratio [OR] 12.2, 95% CI 1.8-83.2; $P = .01$).

Peripheral vascular inflammation and prevalence of MI. Previous MI was documented in 17 of 24 (71%) patients who had an MPOx gradient across the femoral circulation of the affected limb > median vs only 8/22 (36%) of those with lower transfemoral neutrophil activation, and 12/36 (39%) patients with CAD-alone (P for trend <.05) (Fig 2). Also patients with transfemoral IL-6 gradient > median presented a prevalence of previous MI

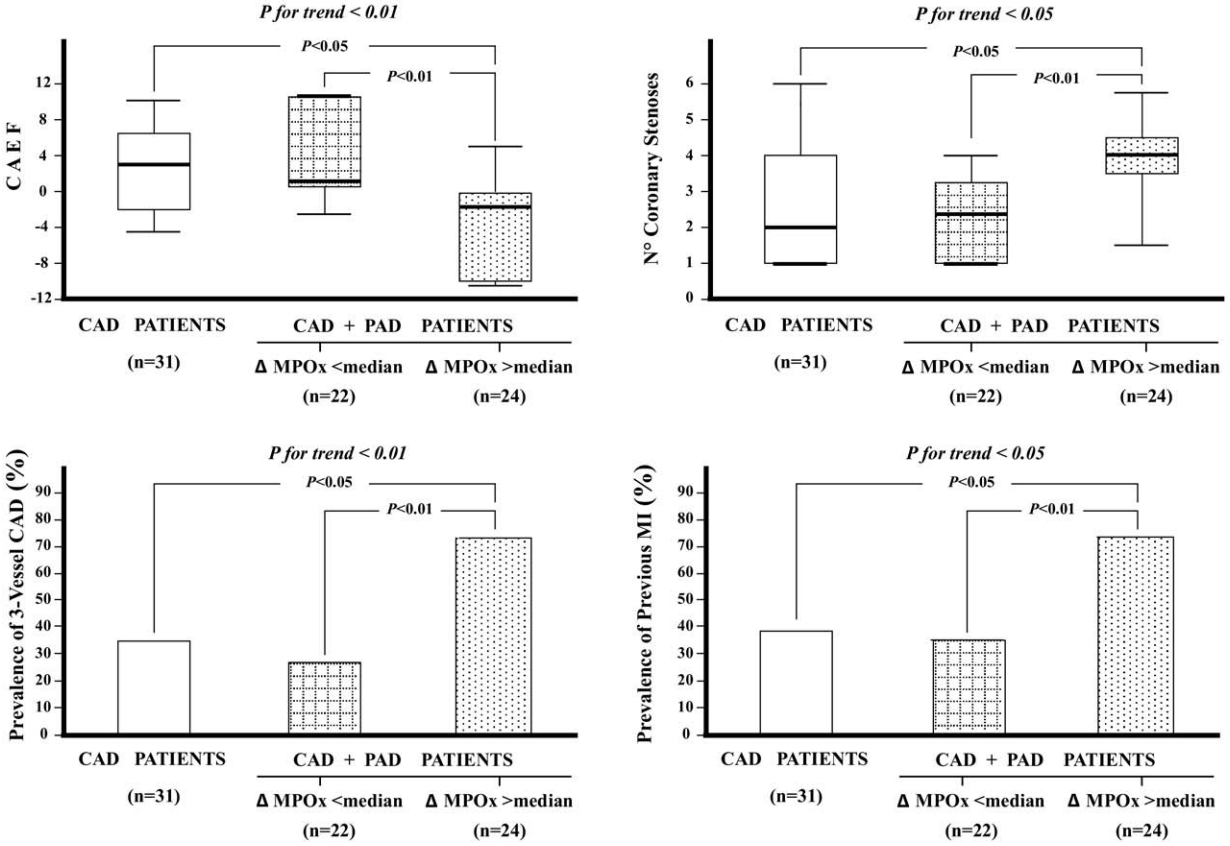

Fig 2. Coronary artery disease (CAD) severity in CAD-alone patients, and in the coronary artery disease + peripheral arterial disease (CAD+PAD) patients divided according to the median value of the transfemoral neutrophil myeloperoxidase (MPOx) content. Data concerning continuous variables (coronary artery endothelial function [CAEF] and number of significant coronary artery stenoses) are expressed as median (10th, 25th, 75th, and 90th percentile) while categorical variables (three-vessel CAD and previous myocardial infarction [MI]) as number of patients (%).

(16/23; 70%) which doubled that in the other groups (39% in both). However, no significant difference was observed at Kruskal-Wallis analysis (P for trend = .25) (Fig 3). Adjusted multivariate analysis showed that patients with transfemoral V-A difference in MPOx > median had roughly a sixfold increased risk of previous MI (OR 5.68, 95% CI 1.15-27.92; $P < .05$).

There was no relationship between the transfemoral V-A differences in hs-CRP and CAD severity.

DISCUSSION

The present study confirms and extends the previous finding that in CAD+PAD increased gradients of neutrophil MPOx content and IL-6 across the femoral circulation of the affected limb are associated with impairment of the coronary arteries.[8] Actually, consistent with the previous report, we found that the transfemoral differences of the two inflammatory markers are strictly related to coronary artery endothelial function. The novel finding of the present report is that when an inflammatory response occurs in the claudicant limb, it is associated with a more severe coronary atherosclerosis as evidenced by (1) a greater number of coronary stenoses; (2) a higher prevalence of three-vessel CAD; and (3) a higher rate of previous MI.

Peripheral vascular inflammation. The increased transfemoral gradients of neutrophil MPOx content and IL-6 observed in the affected limb of CAD+PAD patients was unlikely due to PAD-induced chronic ischemia or impaired shear stress, because the extent of local inflammation did not correlate with ABI, which is a marker of severity of circulatory insufficiency. Consequently, it is conceivable that the local inflammatory response may be related to the presence of active, inflamed plaques, which are common in femoral arteries.[10,11]

The fact that CRP concentration in the blood leaving the affected limb was similar to that observed in the other vascular districts is consistent with a recent study on coronary circulation,[12] and excludes a transfemoral release of this molecule. This suggests that MPOx and IL-6 are more informative than plasma levels of CRP to disclose an inflammatory status in the arterial vessels of the claudicant limb.

Peripheral vascular inflammation and coronary artery endothelial function. Neutrophil activation exerts important pathogenetic activities.[13] In particular, MPOx released

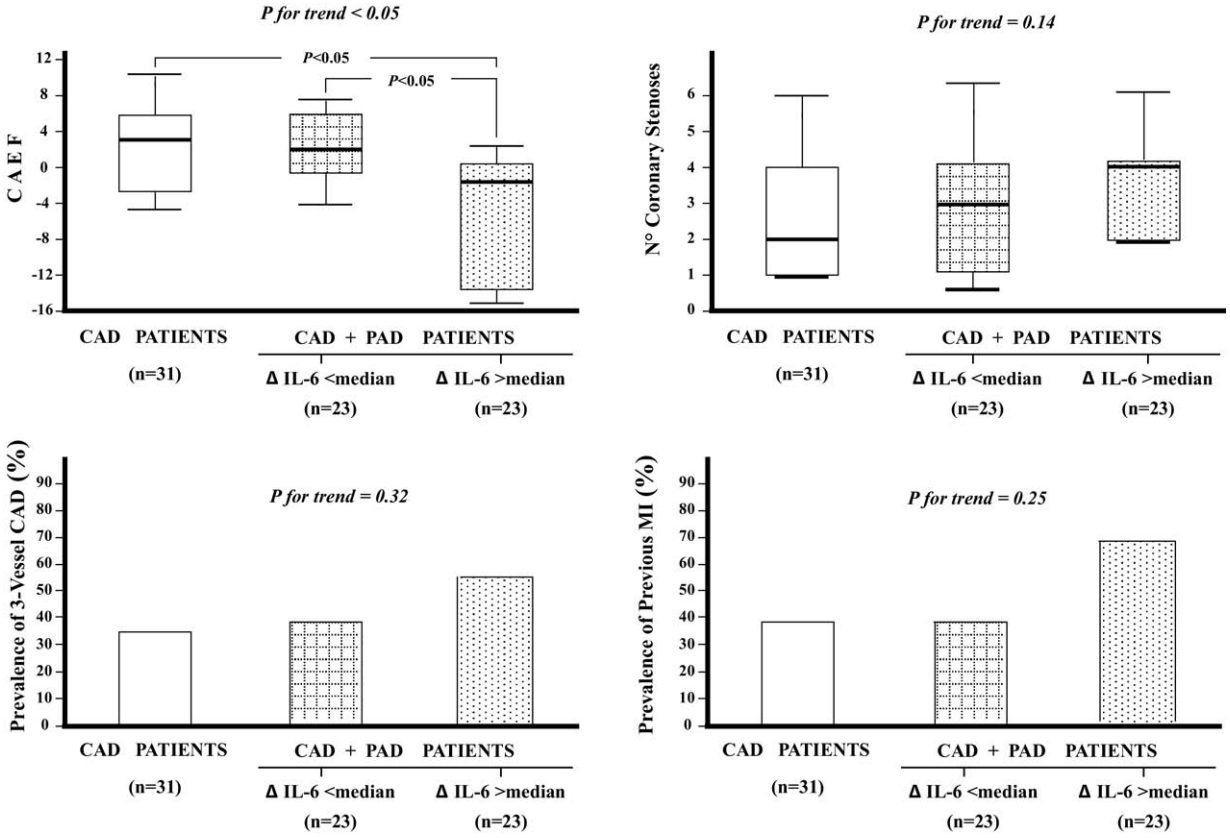

Fig 3. Coronary artery disease (CAD) severity in CAD-alone patients, and in the coronary artery disease + peripheral arterial disease (CAD+PAD) patients divided according to the median value of the venous-arterial difference in interleukin-6 (IL-6) plasma levels across the femoral circulation of the affected limb. Data concerning continuous variables (coronary artery endothelial function [CAEF] and number of significant coronary artery stenoses) are expressed as median (10th, 25th, 75th, and 90th percentile) while categorical variables (three-vessel CAD and previous myocardial infarction [MI]) as number of patients (%).

by neutrophil, as reflected in our study by the reduced neutrophil content of the enzyme, uses nitric oxide as a physiologic substrate, thereby reducing nitric oxide bioavailability.[14] Indeed, serum MPOx levels in humans inversely correlate with brachial artery flow-mediated vasodilation.[15] This, however, reflects a relationship between two systemic measures. Therefore, more indicative of a mechanistic link between inflammation and endothelial dysfunction are the results of the present study showing that a regional non coronary inflammation is associated with a coronary impairment of endothelial function. Indeed, in CAD+PAD patients, the greater the venous arterial difference in neutrophil MPOx content across the femoral circulation of the affected limb (and, thus, presumably the greater the release of MPOx from activated neutrophils), the more severe the endothelial dysfunction in the coronary bed.[8] Also, IL-6 may affect the endothelium,[16] and we found that the transfemoral difference in plasma levels of IL-6 negatively correlated with coronary artery endothelial function.

Noteworthy, coronary vasoreactivity was not related to transcoronary gradient of inflammatory markers, thus excluding that intracoronary vascular inflammation affected coronary artery endothelial function.

Peripheral vascular inflammation and coronary artery atherosclerosis. That in CAD a concomitant PAD entails a more severe coronary artery disease has been widely report.[5-7] Our data, although the cross-sectional nature of this study does not allow us to draw a definitive conclusion about causality, suggest the hypothesis that peripheral vascular inflammation may play a pathogenetic role in CAD. Indeed, we found that CAD+PAD patients with a transfemoral gradient in neutrophil MPOx content > median had a higher number of coronary stenoses and a greater prevalence of three-vessel CAD than those with lower transfemoral neutrophil activation and those with CAD-alone. Furthermore, logistic regression analyses showed that MPOx gradient across the affected femoral circulation remained associated with worse coronary atherosclerosis after adjustment for possible confounders. These findings are in line with previous studies showing that increased systemic levels of MPOx are associated with a high number of coronary stenoses > 50%[17] and are related to CAD severity.[9]

Also, patients with transfemoral gradient of IL-6 > median tended to have a greater prevalence of three-vessel CAD and/or of number of coronary stenoses > 50% than the other two groups, but the difference did not reach the statistical significance. This could be the consequence of the relative small size of our cohort. Indeed, in a previous paper[5] involving 234 patients who underwent coronary angiography, increased levels of IL-6 appeared to be a marker of more severe coronary atherosclerosis.

Peripheral vascular inflammation and prevalence of MI. Another relevant finding of our study is that CAD+ PAD patients with a transfemoral gradient in neutrophil MPOx content > median had a markedly higher prevalence of MI than both those with a lower neutrophil activation across the circulation of the affected limb, and CAD-alone patients. A higher prevalence of MI was observed also in patients with increased release of IL-6 from the affected limb.

CONCLUSION

The conclusions that may be drawn from this hypothesis-generating study are the following: first, in PAD the blood leaving the inflamed claudicant limb contains molecules that may affect coronary arteries. Therefore, PAD, besides being a marker of cardiovascular risk, could have a mechanistic role in the progression of atherosclerosis in coronary arteries. Second, the fact that in CAD the coexistence of PAD is associated with a more severe coronary atherosclerosis may not be generalized to the entire population. Actually, only patients with a marked inflammatory status of the affected limb present a more severe coronary artery endothelial function, a higher number of significant coronary stenoses, a greater prevalence of three-vessel CAD, and previous MI. Although the conclusions suggested by our findings are intriguing, large prospective and possibly non invasive study are required to confirm that the presence of unstable inflamed plaques in the leg arteries portend a worse outcome in PAD.

AUTHOR CONTRIBUTIONS

Conception and design: GB, FP, MC
Analysis and interpretation: VS, GG
Data collection: VS, GG, FS
Writing the article: GB, FP, VS
Critical revision of the article: GB, FP, VS, GG, FS, MC
Final approval of the article: GB, FP, VS, GG, FS, MC
Statistical analysis: GB, FP, VS, GG
Obtained funding: Not applicable
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GB and FP contributed equally to this work.

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